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Function follows form: Spatial structure determines transcription factor activity

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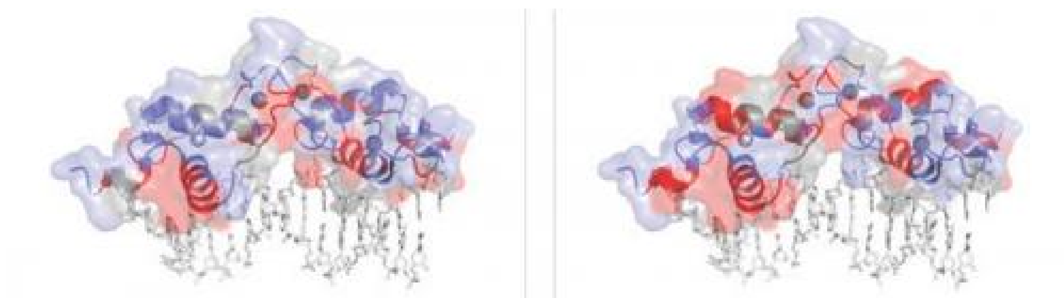

DNA-induced structural changes (parts that change are colored red) in the DNA binding domain of the glucocorticoid receptor (left) and the structural changes (red) that occur when an extra amino acid is inserted in the DNA binding domain of the glucocorticoid receptor as a consequence of alternative splicing (right). Credit: MPI f. Molecular Genetics/Meijsing

Clay can be used in various forms for a range of objects such as cups, plates or bricks. Similarly, proteins can transform their structure and thus adapt their function and activity. Researchers at the Max Planck Institute for Molecular Genetics in Berlin have analysed proteins for such modifications that control gene activity, so-called transcription factors. The researchers thereby discovered that DNA changes the form and the activity of the glucocorticoid receptor, and also ascertained how various domains in the molecule communicate with one another. Furthermore, the way in which the protein domains are connected also changes as a result of the integration of individual amino acids in the protein chain. Different genes are therefore transcribed to varying degrees.

Transcription factors are responsible for transcribing the correct genes and therefore for producing the right quantity of proteins. They bind to specific sections of DNA near genes, such as promoters for example. However, the transcription factors do not function simply as an on/off switch but rather like a volume control, which allows gene expression to be precisely controlled.

The glucocorticoid receptor is a transcription factor, which, for example, is activated by the hormone cortisol during fasting, resulting in glucose production in the liver. Because of its anti-inflammatory effect, it also plays an important role in the treatment of illnesses caused by an overactive immune system, such as allergies, autoimmune diseases and asthma. Various signals determine its activity, two of which are: firstly, the DNA to which the glucocorticoid receptor binds in order to regulate the gene. The second signal is the integration of additional amino acids in the protein.

The Berlin-based Max Planck researchers have studied how these two signals have an effect, which genes are regulated by the glucocorticoid receptor and how they affect the strength of the regulation. "Our findings show that DNA is not simply a passive strip of Velcro which can be bound by proteins. Instead, DNA changes the shape of the proteins and thereby the communication between various protein domains," explains Sebastiaan H. Meijsing from the Max Planck Institute for Molecular Genetics. In this way, the glucocorticoid receptor can adapt its activity to individual genes.

Furthermore, different variants of the glucocorticoid receptor exist. They occur when the original RNA chain, produced when the glucocorticoid receptor gene is transcribed, is subsequently modified again. During this process, known as alternative splicing, additional modules can be added to the amino acid chain in the protein. The modification changes the way in which different sections of the glucocorticoid receptor are connected to one another. As a result, different genes can be transcribed to varying degrees. "Transcription factors are like chameleons in the way they can change their appearance. It allows them to respond to different signals and regulate genes with particular precision," says Meijsing.

More information: Thomas-Chollier, M. et al. A naturally occuring insertion of a single amino acid rewires trancriptional regulation by glucocorticoid receptor isoforms, *PNAS*, 14 October 2013.

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